August 10, 2012

Martha J. Somerman, D.D.S., Ph.D.
Director
National Institute of Dental and Craniofacial Research
31 Center Drive, Room 2C39
Bethesda, MD  20892-2190

Dear Dr. Somerman:

On behalf of our 157,000 members, we are pleased to comment on the National Institute of Dental and Craniofacial Research’s (NIDCR’s) proposed research initiatives for fiscal year 2014. We offer these comments in response to your July 10, 2012, report to the ADA’s Council on Scientific Affairs and your E-Newsletter solicitation of July 13, 2012.

Enclosed you will find our detailed responses to the research initiatives proposed. The proposed initiatives are largely consistent with the biennial research agenda developed by our Council on Scientific Affairs, which highlights clinically relevant critical issues needing scientific exploration. The research agenda is available online at www.ada.org/532.aspx.

We are especially pleased with your proposal to establish more robust measures of clinical outcomes and mechanisms of behavioral interventions for studies of oral diseases and conditions, and to increase the rigor of clinical research by equipping oral health investigators with state-of-the-science measures of outcomes and behavioral intervention mechanisms. Improving how we measure outcomes related to treatment is an especially important component of determining the impact of oral healthcare services and will also aid in the validation of improved therapies.

As a science-based organization, the ADA has a vested interest in ensuring that federal dental research agencies are well funded, their research investments reflect the needs of the dental profession and the knowledge gained advances the oral health of the American public. The research initiatives you have proposed will help advance those goals.

We appreciate the opportunity to comment on NIDCR’s proposed research initiatives for fiscal year 2014. If you have any questions, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org.

Sincerely,

/s/  
William R. Calnon, D.D.S.  
President

/s/  
Kathleen T. O’Loughlin, D.M.D., M.P.H.  
Executive Director

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Comments to the
National Institute of Dental and Craniofacial Research

on the
Proposed Research Initiatives for Fiscal Year 2014

August 10, 2012

A. Developing a Multi-disciplinary Oral Health Research Workforce

The goal of this research theme is to support training of mid- and senior-level investigators to build new oral health or craniofacial research skills and knowledge. There is growing recognition that health challenges require increasingly multi-disciplinary solutions, and that equipping researchers to function in multi-disciplinary teams requires special attention. While there are numerous training opportunities for early-career investigators, training opportunities for mid- and senior-level investigators are less plentiful, and those that are available assume the need for a long-term training experience. For mid- and senior-level investigators, a brief, intensive period of mentoring may be sufficient to equip them with expertise in a new field, methodology, or health condition. To address the need for short-term mentoring for mid- and senior-level investigators in multi-disciplinary research, we propose offering a Career Enhancement Award designed to support and encourage collaborative research projects between mentor and mentee.

Comment:

The Council on Scientific Affairs (CSA) supports this proposal. The CSA agrees that more multi-disciplinary experience in research (as well as in clinical practice) is needed to expand and broaden research on oral health issues. This is consistent with the CSA duty to promote efforts to develop the dental research workforce.

B. Development and Characterization of Animal Models for Studying Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ) presents as an open, persistent area of exposed bone (in the maxilla or mandible) in some patients receiving anti-resorptive therapy for the prevention of osteoporosis, or the treatment of cancers that involve bone. As treatments for these diseases and conditions continue, side effects from anti-resorptive therapies, especially relating to bone, have become increasingly common. Previous NIDCR solicitations have highlighted the need to close the knowledge gap in the cellular and tissue-level pathology of ONJ, and as a result, several animal models have been developed and their refinement is ongoing. In order to develop therapeutics for eventual clinical use in humans, there is a compelling need for these and other animal models to be further developed and fully characterized. NIDCR proposes to develop an initiative with emphasis on developing and characterizing animal models using molecular and imaging tools to allow the research community to test hypotheses on the pathophysiology of this condition. There is currently no early detection methods or therapeutic treatments available to patients suffering from ONJ; development of new prevention and treatment paradigms could improve the quality of life of persons affected by this condition.
Comment:

The CSA agrees that early detection and development of therapies for ONJ is an important need and is consistent the Council’s duties related to therapeutic agents that impact oral health. Developing animal models and understanding the pathophysiology of the condition are necessary steps in the process toward improved patient care.

C. Epigenomics of Viral Associated Oral Diseases

Epigenomics is an emerging field focusing on DNA modifications that result in heritable changes in phenotype and gene expression without changes in the primary DNA sequence. Viral-induced epigenetic perturbations of the host genome, as well as epigenetic changes that occur in the genome of oral viruses play a significant role in the onset and progression of oral diseases. This research theme aims to support research that: 1) describes epigenetic changes and their regulatory roles in cells, tissues and viral components that define oral diseases and their stages of progression; 2) defines the mechanisms by which changes in host and viral gene expression and functionally relevant epigenomic changes weakens the capacity of oral viruses to cause infectious diseases; and 3) defines the mechanisms by which therapies affect host and viral epigenomic modifications to guide clinical interventions. Understanding the mechanisms by which oral viruses induce host epigenomic alterations and clarifying the epigenetic changes that occur in the genome of these viruses can provide novel tools to develop anti-viral therapies for improving oral health.

Comment:

The CSA agrees that this field of research is highly important to a better understanding of oral diseases and the development of effective treatments. This work may help to support the CSA’s interest in expanding dentist’s knowledge of genetics, which the Council believes is necessary to understanding current, and future, therapeutic and disease management strategies. This work may also help to identify and/or explain relationships between oral and systemic diseases and conditions.

D. Establishing Measures of Clinical Outcomes and Mechanisms of Action of Behavioral Interventions for Clinical Trials and Studies of Oral and Craniofacial Diseases and Conditions

This theme would aim to support research to establish more robust measures of clinical outcomes and mechanisms of behavioral interventions for studies of oral diseases and conditions, and to increase the rigor of clinical research by equipping oral health investigators with state-of-the-science measures of outcomes and behavioral intervention mechanisms. Oral health researchers often struggle with selecting rigorous and meaningful outcome measures for clinical studies and/or trials. This includes, but is not limited to, orthodontic outcomes for children with repaired cleft lip / cleft palate, patient-centered outcomes that go beyond the Oral Health-Related Quality of Life Score, and robust measures for behavioral intervention targets. The lack of robust measures of clinical endpoints limits an investigator’s ability to precisely and accurately quantify oral diseases, and the effects of interventions to treat those diseases. Also, without strong measures of the outcomes and mechanisms of behavioral interventions, clinical
research misses opportunities to progress efficiently, building an integrated science of oral health behavior change.

Comment:

The CSA supports this initiative: much work is needed to improve outcome measures, especially in the area of behavioral interventions and mechanisms. This is consistent with the ADA Research Agenda goal to understand the social, behavioral and biological determinants of oral and dental diseases and their impact on the provision of dental care. The Council is also very interested in extending this concept to research on practitioners as well though, as mentioned in this ADA Research Agenda objective: develop, test and validate methods for assessing outcomes related to the use of evidence-based clinical recommendations and clinical practice guidelines in dentistry.

E. Functional Characterization of Oral Cancer Initiating Cells

The overall goal of this proposed theme is to build a knowledge base for developing new targeted and effective therapies for Oral Squamous Cell Carcinomas (OSCC) by elucidating the cellular and molecular properties of Cancer Initiating Cells (CICs) and the composition and architecture of CIC niches. OSCC represent the majority of Head and Neck Cancers with ~38,000 new cases diagnosed each year in the U.S. The survival rates of OSCC patients have not improved significantly during the past few decades, and the unfavorable prognosis is attributed to poor understanding of the molecular and cellular mechanisms of metastatic spread, resistance to therapy, and disease relapse. Studies have revealed the existence of the CICs (sometimes referred as cancer stem cells) in heterogeneous cell populations of human OSCC. It has been proposed that the CICs might be responsible for the metastatic potential as well as resistance to therapy and frequent recurrence of OSCC. Novel therapies designed to target CICs within the bulk of the cancer could provide an effective approach for the treatment of OSCC. While progress has recently been made in the preliminary characterization of oral CICs and their niches, considerable knowledge gaps remain in our understanding of CIC biology. An understanding of the molecular and cellular properties and functions of CICs in greater depth will be vital for the design and development of new targeted and effective therapies that would improve the survival rates of patients with OSCC.

Comment:

The CSA recently discussed its support for focusing more of its resources “integrated oral and systemic health care. The intent is to provide more information and recommendations to clinicians and patients related to cancer and other debilitating diseases that impact oral health. Oral cancer is a significant component of this issue. This theme is also consistent with the ADA Research Agenda goal to understand the biological determinants of oral and dental diseases and their impact on the provision of dental care. The CSA is especially interested in approaches or methods to improve risk assessment and early detection of this debilitating and deadly disease.
F. Osteoimmunomodulation for Oral Bone Healing and Regeneration

The immune system profoundly influences the development of several debilitating oral conditions, such as periodontal disease and peri-implantitis (inflammation around implants), which compromise the integrity of oral bone and its surrounding tissues. The immune system can exert both positive and negative effects on oral bone depending on the state and progression of the disease, as well as the inflammatory, microbial and genetic environment of the host. While recent scientific discoveries have resulted in the identification of several promising therapeutic targets for treatment of inflammatory bone loss, such as small molecules, peptides, stem and progenitor cells and regulatory RNAs, clinical translation of these advances remains challenging because of a paucity of appropriate tools, resources and technologies needed for their clinical implementation. The purpose of this research theme is to encourage translational studies that would leverage recent basic science advances in order to develop treatments for diseases associated with inflammatory oral bone loss. Since periodontal disease and peri-implantitis are primary causes of tooth loss and implant failure, respectively, advances promoted by this initiative will have a positive impact on oral health and other conditions affected by the health of the oral cavity.

Comment:

The time lag from discovery to market for new therapies can be long and costly and so this theme is important with respect to periodontal disease and peri-implantitis. It can take even longer to translate research results on new therapies once developed however. This translation of research results to clinical practice requires effective dissemination of the new information and behavior change. This aspect of research translation requires more focus and study in order to speed the adoption of effective therapies once they have been supported by appropriate research results.

G. The Role of Uncultivable Bacteria in the Oral Microbiome

Oral bacteria, archaea, and fungi exist in the mouth as complex microbial communities arranged within biofilm matrices on both hard and soft tissue surfaces. Each anatomical site contains a unique microbial flora (microbiota). To deepen our understanding of ecological diseases such as caries and periodontitis from the perspective of individual microbial populations, it is essential to understand those microbiotas responsible for maintenance of a normal plaque. Although recent work has revealed the initial events involved with surface colonization and early biofilm progression, little is known about the exact physicochemical, molecular, and metabolic interactions required for long term survival and resilience of biofilms; one persistent challenge in this field has been the need for novel work to understand the role of the large number of uncultivable species in the oral microbial ecology. This initiative aims to: 1) optimize recent technological advances in in vitro culture technologies to enable high through-put analysis of oral biofilms under various experimental conditions; and 2) utilize these newly optimized culture systems to examine mock communities composed of various combinations of known cultivable bacterial species present in the mouth together with newly identified uncultivable species to determine what role, if any, these new species play in the oral microbiome. Information gained through this initiative will also complement on-going work in the Human Microbiome Project by transitioning the field from “what bacteria are present” to “what are they doing” with regard to biofilm assembly, growth, and maintenance.
Comment:

Biofilms are a highly relevant to the two major oral diseases, dental caries and periodontal disease. The last sentence is critical: determining “what are they doing” is the step needed to then ask/answer how we can prevent the negative aspects and/or enhance any positive effects associated with the biofilm.

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Please note, when identifying themes for potential funding initiatives, NIDCR takes many factors into account. These factors include: scientific opportunity, alignment with the mission and goals of the Institute’s strategic plans, robustness of the existing portfolio in a particular theme area, both currently and in the year under consideration, and current budgetary climate.